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Aprosencephaly and Cerebellar Dysgenesis in Sibs

Scott R. Florell, Jeannette J. Townsend, Edward C. Klatt, Theodore J. Pysher, Cheryl M. Coffin, Carl T. Wittwer, and David H. Viskochil

Departments of Pathology (S.R.F., J.J.T., E.C.K., T.J.P., C.M.C., C.T.W.) and Pediatrics (T.J.P., C.M.C., D.H.V.), and Division of Medical Genetics (D.H.V.), University of Utah Health Sciences Center, Salt Lake City, Utah

Aprosencephaly is a rare, lethal malformation sequence of the central nervous system that has been attributed to a postneuralation encephaloclastic process. We describe autopsy findings consistent with aprosencephaly in 2 fetuses conceived from a consanguineous mating (first cousins). Both showed anencephalic manifestations; however, the crania were intact, with fused sutures. The neuropathologic findings were essentially identical. Each fetus had complete absence of the telecephalon and pyramidal tracts, rudimentary diencephalic and mesencephalic structures, primitive cerebellar hemispheres, posterolateral clusters of primitive neural cells in the medullas suggesting an abnormality of neural migration, a normally-formed spinal cord, and retinal dysplasia within normally-formed globes. In addition, both fetuses manifested a peculiar perivascular mesenchymal proliferation seen only within the central nervous system. The similarity of these cases, coupled with parental consanguinity, suggests a primary malformation in brain development due to the homozygous representation of a mutant allele. We hypothesize that these patients may represent a defect in a gene important in brain development, the nature of which has yet to be elucidated.

KEY WORDS: aprosencephaly, atelencephaly, primary malformation, consanguinity, homeodomain, *HOX, OTX-2*

INTRODUCTION

Aprosencephaly is a rare, lethal central nervous system defect characterized by absence of the telecephalon (which gives rise to the cerebral hemispheres, caudate and lentiform nuclei, and olfactory tracts and bulbs), and absence or severe defects of the diencephalon (corresponding to the third ventricle and adjacent structures including the thalamus, hypothalamus, posterior pituitary, optic nerves, and eye). Previously reported cases of aprosencephaly share several findings, including small head circumference with an intact scalp and calvaria (distinguishing aprosencephaly from anencephaly), and absence of the telencephalon, pyramids, and lateral and third ventricles. The remainder of the brain is variably affected, and some authors have used the term "atelencephalic microcephaly" [Garcia and Duncan, 1977; Shewmon et al., 1984; Siebert et al., 1986; Schrander-Stumpel et al., 1988] or "aprosencephaly-atelencephaly" [Lurie et al., 1979; Harris et al., 1994] to describe cases with an absent telecephalon and only mild abnormalities of structures caudal to the third cranial nerves. If genitalia and limb abnormalities are also present, the term "syndrome aprosencephaly" or "XK aprosencephaly syndrome" has been applied [Martin and Carey, 1982; Lurie et al., 1979] (Table I). Aprosencephaly has been attributed to a sporadic, destructive process [Garcia and Duncan, 1977; Adkins and Kaveggia, 1979; Siebert et al., 1986; Towfighi et al., 1987; Kim et al., 1990; Harris et al., 1994]. Siebert et al. [1986] additionally suggested that aprosencephaly is the result of a postneuralation encephaloclastic disruption on the continuum of porencephaly and hydranencephaly. The disruption theory is based, in part, on the lack of identifiable genetic factors; however, Goldsmith et al. [1993] described ring chromosome 13 mosaicism in a case with XK aprosencephaly syndrome, and Towfighi et al. [1987] reported a case of aprosencephaly with 13q− anomaly. In support of the concept that an aprosencephalic phenotype may arise as a primary malformation rather than a random encephaloclastic process, we describe a remarkably similar pair of aprosencephalic sibs conceived by a first-cousin couple.

CLINICAL REPORTS

The mother was a 25-year-old G3 P0021 Hispanic woman with an unremarkable past medical history who had 1 normal daughter by a different father. The father's past medical history was also unremarkable. The family history was notable only for a paternal first

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Address reprint requests to Scott R. Florell, M.D., Department of Pathology, University of Utah Health Sciences Center, 50 North Medical Drive, Salt Lake City, UT 84132.

TABLE I. Reported Cases of Aprosencephaly*

Authors	Chromosome (sex)	Age	Brain wt (g)	Central nervous system	Other notable abnormalities
Lazjuk et al., 1977; Lurie et al., 1979	46,XY	44 weeks	27	Cerebellum normal	Absent thumbs
Garcia and Duncan, 1977	46,XY	2 months	23	Gliomesodermal tissue and calcifications replacing telencephalon, cerebellum well differentiated with irregular-sized folia	Hypoplastic thumbs, absent first toes, cloaca and anogenital opening structures resembling labia minora and clitoris
Iivanainen et al., 1977	46,XY	13.5 months	105	Cerebellum almost normal, with deep furrows between vermis and hemispheres	Hypoplastic penis, bilateral cryptorchidism
Adkins and Kaveggia, 1979	ND (female)	14 months	ND	Cerebellum apparently normal, but small by CT	Calvarium appeared to be absent, extreme hypotelorism
Lurie et al., 1980	46,XY	Term	28	Telencephalic and diencephalic remnants found, cerebellum with dysplastic gyri and absent nuclei	Absent thumbs
Martin and Carey, 1982	46,XX	35 weeks	8	Cerebellum normal, absent globes	Atrial septal defect, atresia ani
Shewmon et al., 1984	46,XX	2 months	ND	Cerebellum ND	Spina bifida
Siebert et al., 1986	ND (female)	21 weeks	7	Cerebellum nearly normal, small nodules of undifferentiated cells in forebrain	Left diaphragmatic hernia
Young et al., 1986	46,XX	33 weeks	ND	Cerebellum normal	Sirenomyelia, absent upper trachea, absent kidneys, ureter, and bladder
Towfighi et al., 1987	46,XY,del(13)(q22q31)	20 months	ND	Cerebellum grossly normal with intracytoplasmic cellular inclusions, calcification, and abundant gliomesodermal tissue	Bilateral cryptorchidism
Schrander-Stumpel et al., 1988	ND (male)	15 months	ND	Atelencephaly by CT, cerebellum ND	Other abnormalities not reported
Townes et al., 1988	46,XX	36 weeks	ND	Cerebellum normal by CT	Absent thumbs, limb underdevelopment
Kim et al., 1990	ND (female)	39 weeks	40	Hypoplastic cerebellum, calcific vasculitis	Absent left thumb, rudimentary adrenal glands, abnormal kidneys, spleen, and genitalia
Goldsmith et al., 1993	45,XY,−13/46,XY,r(13)	38 weeks	10.4	Cerebellum ND	Ventricular septal defect agenesis of right and hypoplasia of left kidney, agenesis of right and cryptorchid left testicle, rudimentary left thumb, bilateral clubfeet
Harris et al., 1994, case 2	46,XX	19 weeks	3.9	Cerebellum recognizable	Limb underdevelopment, absent left thumb, cleft palate, malrotation and foreshortening of gastrointestinal tract, dysplasia of right adrenal and gonad
Harris et al., 1994, case 1; Florell et al., case 1	46,XY	25 weeks	5	Severe cerebellar dysgenesis, foci of primitive neurons in medulla, perivascular mesenchymal proliferation in CNS, retinal dysplasia	Bilateral clinodactyly fifth digit, camptodactyly fourth digit (left), inapparent nipples, see Table II
Florell et al., case 2	Not done (female)	25 weeks	3.9	Severe cerebellar dysgenesis, foci of primitive neurons in medulla, perivascular mesenchmal proliferation in CNS, retinal dysplasia	Bilateral clinodactyly fifth digit, camptodactyly fourth digit (left), bifid uvula, see Table II

*CT, computed tomography; ND, not described; CNS, central nervous system.

cousin with mental retardation of unknown cause. Patient 1 was reported previously as "Case 1" by Harris et al. [1994].

Patient 1

This pregnancy was terminated by dinoprostone induction at 25 weeks of estimated gestation after an ultrasound examination at 21 weeks of gestation documented an abnormal cranium interpreted as anencephaly. The prenatal course until this point was unremarkable and an ultrasound study at 14 weeks was interpreted as normal, although the brain was poorly visualized. The maternal serum alpha-fetoprotein (MSAFP) was normal for gestational age. Routine G-banding chromosome analysis from cord blood showed a 46,XY karyotype without apparent structural abnormalities.

Autopsy showed a 25–26-week gestational-age fetus based on foot length (4.3 cm). The placenta was grossly normal, but the three-vessel umbilical cord was only 24 cm long (expected mean length at 25 weeks of gestation, 40 cm [Naeye, 1985]). External examination showed marked diminution of the head circumference with an abruptly-sloping forehead above normally formed but protruding eyes (Fig. 1), micrognathia with wide gums and a narrow palate, clinodactyly of the fifth digits, camptodactyly of the left fourth digit, inapparent nipples, hypoplasia of the scrotum, and a nonreducible equinovarus deformity of the right foot. Palmar and digital flexion creases were normally formed. Thoracic and abdominal viscera were grossly and histologically normal, and the anus was patent. Gonads were intraabdominal (Table II).

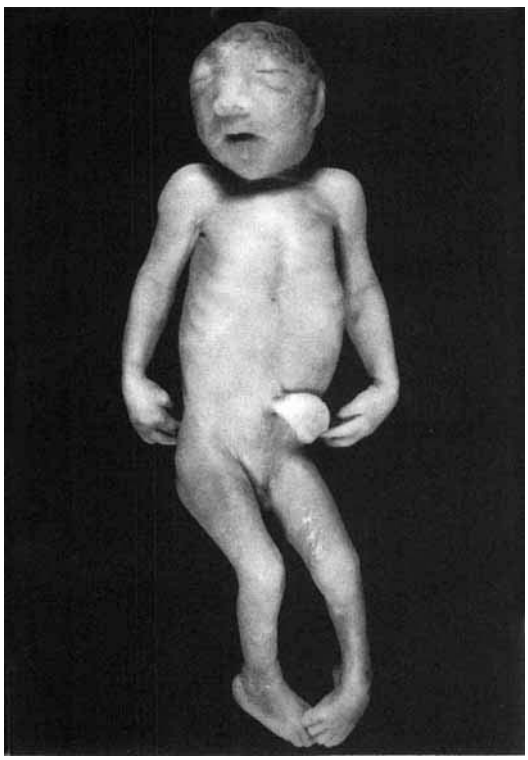

Fig. 1. Patient 1, 25-week gestational age, front view. Note marked diminution of head size, abruptly-sloping forehead, and talipes equinovarus.

The fetus had a normal scalp and intact cranium, but the fontanels were closed and all cranial sutures were apparently fused. The anterior and middle cranial fossae were markedly reduced in size, and the posterior fossa was funnel-shaped. The cerebral hemispheres were absent, and a 0.6-cm mass of soft, gelatinous tissue was present in the anterior fossa. Two small, lateral spherules in the posterior fossa were reminiscent of cerebellar hemispheres, but no vermis was present. The brain stem, fourth ventricle, and spinal cord were grossly normal. The cranial contents weighed 5.0 g (expected mean brain weight at 25 weeks, 92 ± 31 g [Singer et al., 1991]; Fig. 2).

Serial sections of the cranial contents demonstrated fragments of normal-appearing choroid plexus with adjacent loose mesenchymal tissue rostrally, but no cerebral cortex, white matter, olfactory structures, or area cerebrovasculosa. Caudally, nodules of neurons resembling basal ganglia were covered superiorly by remnants of ependymal cells. A central cleft lined by ependyma suggested a rudimentary third ventricle, and nests of neurons were present in the neuropil adjacent to the cleft. Sections of midbrain demonstrated a patent aqueduct, and structures consistent with third nerves exited inferiorly, but there were no recognizable peduncles or substantia nigra. The pons was poorly formed but demonstrated middle cerebellar peduncles adjacent to the dentate nucleus. Focal collections of neurons lateral to the dentate were suggestive of a very primitive cerebellar anlage. The medulla contained identifiable inferior olives beneath a fourth ventricle and scattered clusters of primitive neurons with immunohistologic reaction for vimentin, S-100, leu7, synaptophysin, and neurofilament, but no staining with glial-filament acid protein. These cells were present at the posterolateral aspect of the medulla (Fig. 3; Table IV). No pyramids were present. The spinal cord was normal. No olfactory structures were identified. All sections showed a prominent mesenchymal proliferation around small vessels within the parenchyma of the brain and spinal cord (Fig. 4; Table IV), but the somatic vasculature was histologically normal.

The eyes were normally formed, and histologic examination showed retinal dysplasia manifested by numerous rosettes and minimal gliosis. The optic nerve head and optic nerve were rudimentary, with little normal architecture (Table III).

Patient 2

This pregnancy was terminated by dilation and evacuation at approximately 25 weeks of gestation, after an ultrasound study at 22 weeks demonstrated an intact cranium with a very small head circumference and the possibility of an intracranial abnormality similar to that of the previous sib. The prenatal course was otherwise unremarkable. Chromosome studies were not done. The MSAFP was normal.

Autopsy showed a morcellated fetus of approximately 25 weeks of gestation based on foot length. The

TABLE II. General Autopsy Findings

	Patient 1	Patient 2
External		
General	Male fetus	Highly morcellated female fetus D & E specimen
Gestational age, foot length	25–26 weeks	25 weeks
Crown-heel length (cm)	27.5	Unknown, fragmented
Body weight (g)	451	185 (aggregated fetal tissue)
Foot length (cm)	4.3 bilateral	4.4 bilateral
Head		
Cranium	18.2 cm OFC Flattened Synostosis of sutures Fontanels closed	17.4 cm OFC Flattened Synostosis of sutures Fontanels closed
Mandible	Small	Small
Palate	Wide gums; narrow palate	Bifid uvula
Limbs		
Hands	Bilateral clinodactyly fifth digit Camptodactyly fourth digit, left Normal flexion creases	Bilateral clinodactyly fifth digit Camptodactyly fourth digit, left Normal flexion creases
Feet	Nonreducible equinovarus	Abnormal plantar flexion creases
Thorax	Inapparent nipples	Unknown
Abdomen	Unremarkable	Unknown
Genitalia	Male Hypoplastic scrotum	Female, unremarkable
Anus	Patent	Unknown
Internal[a]		
Pelvis	Intraabdominal testes	Uterus, vagina normal Ovaries not identified
Placenta	Normal for gestation	Normal for gestation
Umbilical cord	24 cm	Unknown, fragmented

[a] Internal status of the thorax and abdomen was unremarkable in both cases.

aggregated mass of identifiable fetal tissue weighed approximately 185 g, but due to the fragmented nature of the specimen an accurate umbilical cord length could not be determined. The head was small and consisted of two fragments: the cranium and maxilla were intact and symmetrical, but the forehead sloped acutely into the flattened calvaria. The uvula was bifid. The separate mandible appeared small. There was bilateral clinodactyly of the fifth digits and camptodactyly of the left fourth digit. Palmar and digital flexion creases were normally formed. The thoracic and abdominal viscera were grossly and histologically normal (Table II).

The scalp was intact, and the cranial sutures were fused and the fontanels closed. The anterior and middle fossae were small and asymmetric, and the posterior fossa was funnel-shaped. The anterior fossa contained a small amount of tan, fibrous tissue in the midline, with a 0.5-cm fragment of soft, tan tissue adherent to the fibrous tissue. Cerebral hemispheres were not present. The middle fossa contained a smooth mass of tan tissue with no identifiable landmarks. Under a thickened tentorium, the posterior fossa contained smooth, rounded projections on either side of the midline, reminiscent of cerebellar hemispheres. The medulla and spinal cord appeared grossly normal. Cranial contents weighed 3.9 g.

Serial histologic sections of the cranial contents demonstrated fragments of choroid plexus, but no cerebral cortex, white matter, or olfactory structures. More caudally, clusters of neurons suggested dysplastic basal ganglia. A substantia nigra could not be identified. The pons contained a recognizable tegmentum and atretic basis pontis. Only one dentate nucleus was identified, with surrounding smaller collections of poorly orga-

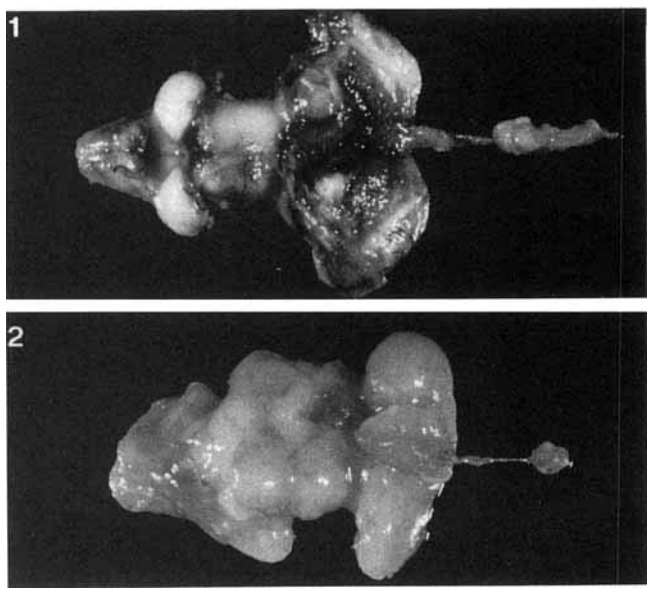

Fig. 2. Gross appearance of cranial contents of patients 1 and 2. Note absence of cerebral hemispheres and recognizable landmarks (ventral view; rostral to right).

nized neurons consistent with primitive cerebellar anlage. The medulla was recognizable but asymmetric, and pyramidal tracts were absent. Two clusters of primitive neurons with identical immunohistochemical staining patterns (Table IV) were present at the periphery, similar to findings in the previous sibling (Fig. 3). Mesenchymal proliferation around small vessels in the brain and spinal cord was seen in all sections (Fig. 4; Table IV), but was not present in somatic vasculature.

The eyes were normally-formed, but there was retinal dysplasia manifested by numerous rosettes. The optic nerve was mildly atrophic, but otherwise histologically normal. The anterior and posterior pituitary were well-formed (Table III).

DISCUSSION

The gross and histologic findings in both cases fulfill traditional criteria for aprosencephaly, and are the first-reported full sibs with this condition. The similarities between these cases are striking and differ from other reported cases of aprosencephaly in which the structures caudal to the telencephalon, including the cerebellum, were either normal or mildly malformed. In contrast, the diencephalon, mesencephalon, and cerebellum in these two patients were markedly abnormal and primitive. Both patients manifested unique histologic findings of perivascular mesenchymal proliferation and clusters of primitive neurons in the posterolateral medullas which have not been previously described. These consistent findings, coupled with an autosomal-recessive inheritance pattern, suggest that this variant of aprosencephaly is a primary malformation due to a single gene defect.

The pathogenetic mechanism of aprosencephaly has remained speculative since the first reported case by Lazjuk et al. [1977]. The facial changes and sloping forehead were suggestive of anencephaly; however, the skull showed a normal complement of cranial bones with fused sutures, eliminating a neural tube closure defect. Siebert et al. [1986] suggested that aprosencephaly and atelencephaly belong to a series of postneuralation encephaloclastic disorders, including porencephalic cyst and hydranencephaly. According to this paradigm, the development of the brain proceeds normally until a catastrophic event such as the loss of vascular supply occurs, causing secondary destruction of the brain parenchyma. Other authors have observed histologic findings suggestive of a destructive process such as calcospherites, calcific vasculitis [Kim et al., 1990], and gliomesenchymal scar tissue [Iivanainen et al., 1977; Towfighi et al., 1987].

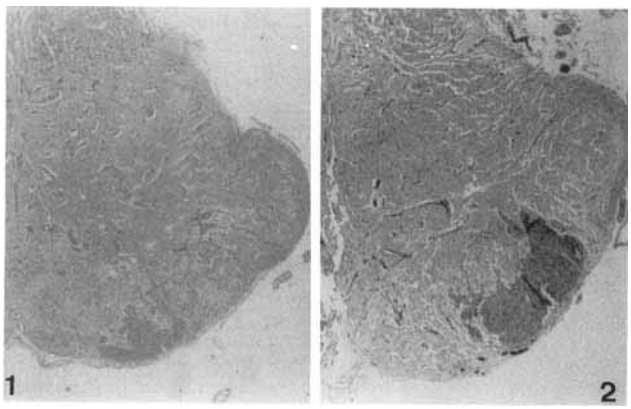

Fig. 3. Histologic appearance of primitive neuron clusters at posterolateral periphery of medullas from patients 1 and 2 (hematoxylin and eosin, ×20).

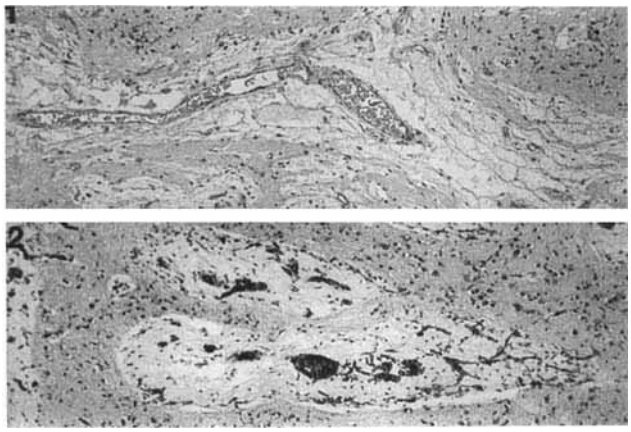

Fig. 4. Histologic appearance of blood vessels in patients 1 and 2, showing striking perivascular mesenchymal proliferation. Note that the vessels lumina do not appear compromised. Somatic vasculature was normal (hematoxylin and eosin, ×200).

The first of the two cases presented here was previously hypothesized to be the result of an encephaloclastic process [Harris et al., 1994] related to a proliferative vasculopathy. The authors speculated that an autosomal-recessive proliferative vasculopathy may have resulted in a disruptive sequence that destroyed the developing forebrain. This explanation is supported by the report of Harper and Hockey [1983], in which two cases of hydranencephaly-hydrocephaly syndrome showed a proliferative vasculopathy that was the putative cause of severe brain abnormalities. In those cases, the authors described "glomeruloid" vessels with endothelial hyperplasia which compromised the vascular lumen, resulting in focal ischemia and destruction of the developing forebrain. The patients described here showed perivascular mesenchymal proliferation, but no endothelial hyperplasia or compromise of the vessel lumina. Ectopic foci of primitive neurons occupied the same posterolateral sites in the medullas of both cases. This suggests an abnormality of neural migration that could not simply be explained by a sporadic encephaloclastic process. We hypothesize that these cases are a result of a primary malformation due to the homozygous representation of a mutant allele for a gene important in early brain development.

The plausibility that a single gene defect could lead to this variant of aprosencephaly is supported by the paradigm of vertebrate homeobox (*HOX*) genes that have specific spatiotemporal expression patterns, and that define the development and differentiation of par-

TABLE III. Central Nervous System Findings

	Patient 1	Patient 2
Brain weight (g)	5	3.9
Meninges	Thickened	Thickened
Telencephalon	Cerebrum absent	Cerebrum absent
Olfactory bulbs, tracts	Absent	Absent
Diencephalon		
Optic nerve	Rudimentary	Mildly atrophic
Optic chiasm	Absent	Absent
Neurohypophysis	Absent	Present
Eye	Well-formed; retinal dysplasia	Well-formed; retinal dysplasia
Oculomotor nerve	Present	Absent
CN 4–12	Absent	Absent
Mesencephalon	Absent	Absent
Metencephalon		
Pons	Poorly-formed	Poorly-formed Atretic basis pontis
Cerebellum	Dentate present Rudimentary	Dentate present Rudimentary
Medulla	Present Foci of primitive neurons Pyramids absent	Present, asymmetric Foci of primitive neurons Pyramids absent
Spinal cord	Present	Present
Perivascular mesenchymal proliferation	CNS, spinal cord	CNS, spinal cord

ticular axial segments. *HOX* genes consist of more than 30 genes arranged in four clusters (*HOX* A–D) on four different chromosomes [Wright, 1991]. These genes are highly conserved, and encode proteins with DNA-binding domains consisting of approximately 60 amino acids that generally function as transcriptional factors [Wilkinson, 1989]. Evidence suggests that the genes are expressed in a sequential fashion, from anterior to posterior body regions. In the central nervous system, *HOX* genes are expressed in the hindbrain and spinal cord, but are not expressed in the forebrain or midbrain [Wilkinson, 1989]. In recent years, several analogous homeodomain-containing genes have been described and appear to play a crucial role in the development of the prosencephalon.

The neuromeric model of the organization of the embryonic forebrain as put forth by Puelles and Rubenstein [1993] is based on studies of multiple homeodomain-containing genes expressed in mouse and chicken embryos in regionally restricted patterns at various stages of embryogenesis. This model is designed to provide an anatomic framework for studies of forebrain development. It divides the mammalian forebrain into six transverse domains known as prosomeres, p1–6. Prosomeres p1–3 become the diencephalon, and p4–6 become the secondary prosencephalon, where the ventral region consists of the hypothalamus, and the dorsal aspect consists of the telencephalic vesicles. This prosomeric model directed our search to identify a defective gene that could

TABLE IV. Immunohistochemical Staining Pattern

Stain	Marker of:	Cell clusters, rhombencephalon	Perivascular proliferation
Smooth muscle actin	Smooth muscle, myoepithelial cells	–	–
Vimentin	Mesenchymal cells	+	+
Desmin	Smooth, striated muscle, myofibroblasts	–	–
Muscle-specific actin	Muscle cells	–	–
Collagen IV	Basement membrane	–	–
Factor VIII	Endothelial cells	–	–
CD34	Endothelial cells	–	–
Ulex europaeus	Endothelial cells	–	–
Glial fibrillary acid protein (GFAP)	Astrocytes, ependymal cells, oligodendrocytes	–	–
S-100	Glial and Schwann cells	+	–
Synaptophysin	Neurons	+	–
Neurofilament	Neurons	+	–
Leu7 (CD57)	Primitive neural and glial cells	+	–

account for the aprosencephalic variant malformation in these two patients. Orthodenticle (*otd*), a homeodomain-containing gene, is one of three known genes that play a major role in central nervous system and head development in *Drosophila melanogaster*. Both mouse (*Otx1, Otx2*) and human (*OTX1, OTX2*) homologues to the *otd* gene have been isolated and characterized. In the mouse, the two *Otx* genes are expressed in the basal telencephalon, diencephalon, and mesencephalon, but not in spinal cord [Simeone et al., 1993]. Intuitively, mutations in early developmental genes encoding transcription factors controlling the expression of other genes may have catastrophic effects on brain development, and could theoretically produce a wide spectrum of brain abnormalities suggestive of an encephaloclastic process. An *Otx* mouse mutant has not been identified, although an example of an apparent encephaloclastic-like phenotype is shown in the *Lim1* mouse. Mice that were homozygous for the null allele of the homeodomain gene, *Lim1,* lacked head structures anterior to the otic vesicle, but showed normal development of the trunk and tail regions [Shawlot and Behringer, 1995].

The prosencephalon, mesencephalon, and rostral rhombencephalon were selectively affected in the two fetuses described here, which matches the expression profile of *OTX2*. Therefore, we screened the *OTX2* gene for mutations in DNA from formalin-fixed paraffin-embedded tissue from both fetuses. By PCR analysis, the *OTX2* gene was present, and no sequence variations were identified [Florell and Viskochil, unpublished results]. Nevertheless, assuming that the prosomeric model described by Rubenstein et al. [1994] may be applied to other vertebrates, we predict that homozygous representation of mutant alleles for other genes that are both regionally and temporally expressed in the brain during embryogenesis could cause the severe brain malformations observed in these two cases.

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NOTE ADDED IN PROOF

After this manuscript was accepted for publication, the phenotype of the $Otx2^{-/-}$ mouse was published [Acampora et al., 1995]. Mutation of both *Otx2* alleles resulted in the loss of the forebrain and midbrain. The phenotype of the hindbrain was variable. While similar to our cases, the mutant mouse brain embryos also showed deleted eye anlage, unlike our cases in which the globes were well formed.

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